IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

ROBERT T. LAWTON, et al.

Appl. No. 09/281,760

Filed: March 30, 1999

For: **SPECIFIC BINDING PROTEINS FOR TREATING CANINE ALLERGY**

Art Unit: 1643

Examiner: Ewoldt, G.

Atty. Docket: 03604-0002-US01

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INVENTOR'S DECLARATION UNDER 37 CFR § 1.132

Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Gregory Francoeur, hereby declare as follows:

1. I am a co-inventor in the above-captioned application and familiar with the subject matter claimed therein.

2. I have been a Research Associate II at IDEXX Laboratories, Inc., in the Division of Research and Development, Department of Molecular and Cellular Biology since June 1996.

3. I am skilled in the art relating to the invention described in the above-captioned patent application. I am a PhD candidate in Molecular Immunology at the University of Maine at Orono. I have a Masters degree in Applied Immunology from the University of Southern Maine (May 1996).

CERTIFICATE OF MAILING
(37 C.F.R. §1.8a)

I hereby certify that this paper (along with any referred to as being attached hereto) is being deposited with the United States Postal Service on the date shown below with sufficient postage as First Class Mail in an envelope addressed to the Commissioner for Patents, Washington, D.C. 20231.

February 26, 2001
Date

C Marquez
Name Cynthia Marquez

4. I have reviewed the Office Action of October 24, 2000 regarding the above-captioned patent application. Regarding ¶¶ 5 and 6 of the Office Action, the Examiner had rejected claims 6-11, 15-17, 21, 23, 27-30, 34-37 and 43 under U.S.C. § 112 because the specification did not reasonably provide enablement for the composition or method of the claimed invention. Specifically, the Examiner objected to the use of the phrase "a leucine positioned two peptide bonds away from a tyrosine-arginine pair." The Examiner contended that the specification provided insufficient working examples that the claimed specific binding protein actually binds all approximately 1600 possible epitopes encompassed by the claim.

5. I have reviewed the data in the specification, as well as data from Phage Display Experiments (Exhibit A) regarding the above-captioned application. For reasons that I explain in detail below, I believe that the specification in the above-captioned application, as well as the Experimental data disclosed in Exhibit A, provides sufficient evidence to support the claimed invention.

6. The claimed invention is directed towards a conserved peptide motif which binds to the specific binding protein disclosed in the specification. Specifically the peptide motif is Leu-Xaa-Xaa-Tyr-Arg or Leu-Xaa-Xaa-Tyr-Arg-Xaa-Xaa-Leu. Phage Display experiments have shown that there are many peptides with the conserved motif above that bind to the specific binding protein. Exhibit A is a portion of the Phage Display results that were sequenced, and provides a linear comparison of 7-mer peptide sequences which bind to the specific binding protein. Briefly, pools of phage clones were tested for inhibition of native or recombinant IgE binding to the specific binding protein. As can be seen, there is conservation present between the native canine IgE and phage display peptides isolated in the Leu and Tyr-Arg positions. However, when comparing the type of amino acid substitutions taking place between the

different peptides, it is apparent that non-conservative substitutions are taking place in the flexible region of the peptide. For example, the amino acid position after the conservative leucine is changed from a threonine in the native sequence, to leucine or glutamic acid. Likewise, the tryptophan residue before the conserved tyrosine is changed to leucine, valine or glutamic acid. All of these changes are non-conservative, ranging from 1-6 on a similarity scale of 25. That non-conservative substitutions, as defined by Dayhoff Mutation Matrix amino acid similarity values (Dayhoff, "Atlas of protein sequence and structure", 1968, Chapter 4), are taking place indicates the non-critical nature of the amino acid positions (Geysen et al, "Cognitive Features of Continuous Antigenic Determinants", 1989).

7. In addition to the data presented in Exhibit A, the specification also provides evidence in support of the claimed invention. The specification provides that a 7 amino acid phage display peptide (SEQ ID NO:4) inhibits binding of the specific binding protein to either native or recombinant canine IgE (SEQ ID NO:10). A comparison of the sequences is shown below:

Thr-Leu-**Leu-Glu**-Tyr-Arg-Met (SEQ ID NO:4)

Gly-Met-Asn-Leu-**Thr-Trp**-Tyr-Arg-Glu-Ser-Lys (SEQ ID NO:10)

As seen, the Leu-to-Thr and Glu-to-Trp substitutions are both highly non-conservative changes, having similarities from 1 to 6 on a scale of 25. This, combined with the phage display data above, supports our contention that non-conservative amino acids can be substituted into the non-critical region between leucine and tyrosine-arginine.

8. The specifications also provide data showing that a change in the conserved motif ablate specific binding protein binding to the peptide. Experiments were performed which demonstrated a single amino acid substitution of the canine IgE sequence, which changed the

Tyr-Arg group to Ser-Arg, completely ablated binding of the synthesized peptide to the specific binding protein (pg. 36, lines 11-19). The Tyr to Ser substitution is also non-conservative, giving a similarity score of 5 on a scale of 25. Thus, a non-conservative amino acid change gives rise to a different result in these experiments. This demonstrates the critical nature of the tyrosine residue, and distinguishes the non-critical nature of the amino acid residues between the Leu and Tyr-Arg groups.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

DATED: 2.23.2001

Greg Francoeur

EXHIBIT A: DNASIS Analysis of Phage Display Peptides Binding to Monoclonal Antibody 8H.8

LIBRARY	SEQUENCE OF DISPLAYED PEPTIDE	ISOLATE
PhD7	T **L** L E **Y** **R** M	2028-32
PhD7	T **L** L V **Y** **R** L	2028-35
PhD7	T **L** L L **Y** **R** L	2028-35
PhD7	T **L** E L **Y** **R** L	2028-35
	G M N **L** T W **Y** **R** E S K	Canine IgE